

Customer No. 31,834

Attorney Docket No. BR029-US-02

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FEB 26 2008****REMARKS**

Claims 1-52 are pending in this application. Claims 1-15 and 33-46 were withdrawn from consideration by the examiner

**Rejections Under 35 U.S.C. § 102**

Claims 15-32 and 47-52 were rejected for alleged anticipation by Tournier et al US 6,042,809 ("the '809 patent"). Applicants respectfully disagree. Applicants invention is based on the finding that gas-filled microvesicles obtained by reconstituting a dried composition in the presence of a gas, by contacting it with an aqueous carrier, have advantageous features when the gas in contact with is at reduced pressure (i.e. a pressure lower than atmospheric pressure).

The reduced pressure referred to in the description and in the relevant claims is the pressure of the gas before reconstitution of the suspension of gas-filled microvesicles. Once the suspension is reconstituted, the whole content of the vial (including the gas in the bubbles) will necessarily be at atmospheric pressure (see page 31, lines 14-18).

In contrast, the '809 patent neither teaches nor suggests the use of gas of lower than atmospheric pressure in preparing microvesicles. For instance, in Example 1, in particular col. 8, line 66 to col. 9, line 2, states that vials containing the dried material are first closed with a rubber stopper and evacuated under vacuum and then the gas is introduced into the vials via a needle through the rubber stopper. The fact that no particular measure is taken to control the pressure of gas after its introduction into the vial makes clear that the gas is at atmospheric pressure. See also, Col. 7, line 65 to col. 8, line 2. Thus, the '809 patent cannot anticipate the instant claims.

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Applicants note that the Examiner's contention that the '809 patent teaches microvesicles containing gas at reduced pressure is not only irrelevant to Applicants claims, but also incorrect.<sup>1</sup> The microvesicles in the '809 patent are clearly reconstituted at atmospheric pressure and then external pressure is applied to evaluate their stability. The  $P_c$  value (i.e. the value of pressure chosen to define the resistance of bubbles to external pressure) has no relation at all to the pressure of the gas inside the bubbles or to the pressure of the gas prior to reconstitution.

#### Rejections Under 35 U.S.C. § 103

Claims 16-32 and 47-52 were rejected for alleged obviousness over the '809 patent in view of H. Van Liew, J. App. Physiol. 82:2045-2053 (1997) ("Van Liew article"). Applicants note that the subject matter of the '809 patent and the instant claims were at the time of invention subject to an obligation of assignment to the same entity; thus, the '809 patent is not proper art for use in an obviousness rejection.

Moreover, as explained above, the '809 patent does not disclose or suggest contacting dried material with gas at a reduced pressure. The Van Liew article fails to remedy

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<sup>1</sup> In particular, table 1 cited by the Examiner discloses the pressure values ( $P_c$ , critical pressure) at which half of the original gas-bubbles are destroyed.  $P_c$  is discussed in detail in EP 554213 (see fig. 1 on page 5 and subsequent discussion on pages 5 and 6). From the discussion in EP554213, it is clear that  $P_c$  is an external pressure applied to the bubbles, to evaluate their resistance to said external pressure; the higher the measured  $P_c$  value, the higher the bubbles stability (in the case of EP554213, said stability to external pressure depends also from the kind of selected gas). It has no bearing on the pressure of the gas prior to reconstitution or the pressure of the gas inside the microvesicles upon reconstitution.

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this deficiency. Like the '809 patent, the Van Liew article fails to teach or suggest use of gas at reduced pressure in preparing microvesicles.<sup>2</sup>

Thus, even in combining the teachings of the '809 patent with those of Van Liew, which Applicants submit is improper, the skilled person would not have arrived at the instantly claimed invention.

### The Double Patenting Rejections

Claims 16, 21-24, 28-32 and 47-52 were rejected for alleged obviousness-type double patenting over US Patent Nos. 6485705, 6403057, 6896875, 6592846, 6613306, 6187288, 6042809, 5911972, 6183725 and 6136293 in view of the Van Liew article.

Claims 16, 21-24, 28-32 and 47-52 were provisionally rejected for alleged obviousness-type double patenting over the claims of US Application Nos. 10/544123, 10/584327, 10/584,382, 10/725777, 10/831165, 11/058169, 11/202008, 11/660188, 11/851769 in view of the Van Liew article.

<sup>2</sup> The Examiner asserts that Van Liew discloses bubbles with negative pressure inside, i.e. a pressure lower than the pressure in the surrounding medium. As explained above, the pressure of the gas inside the microvesicles after reconstitution is irrelevant to Applicants claims. Moreover, the Examiner's assertion appears to be based on a misinterpretation of the statement on page 2045 col. 2, lines 24 and ff.: "The crucial aspect of a structural stabilizer is that it must produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside, especially to counter the strong positive internal pressure due to surface tension when the bubbles are small".

The above negative pressure cannot however be intended as an "absolute" negative pressure (in the sense that the pressure inside the bubble is lower than the pressure in the surrounding medium, i.e. atmospheric pressure in this case), but rather as a pressure which counters (i.e. having an opposite direction) the internal overpressure (with respect to the surrounding pressure) caused by surface tension at the gas-liquid interface.

This becomes clear by reading the subsequent mathematical explanation across page 2046. As a matter of fact, it is clear that the presence of the stabilizer is intended to act as a counterpressure ( $P_r$ ) against the hydrostatic pressure ( $P_h$ ) exerted by the surface tension (col. 2 first paragraph). Without the stabilizing layer, the gas contained in the bubble will be forced to diffuse outwardly, because of this hydrostatic pressure. The fact that the counterpressure exerted by the stabilizer is considered by the author a "negative pressure" (opposing to the "positive" hydrostatic pressure) is only a matter of mathematical convention, to indicate its direction with respect to the hydrostatic pressure, as inferable from equation 3 at the bottom of page 2046, col. 2. In said equation, the hydrostatic pressure " $P_h$ " appears as a positive value, while the counterpressure " $P_r$ ", generated by the stabilizer, is indicated as a negative pressure.

It is clear from the above that the aim of the "negative" pressure generated by the stabilizer is thus that of balancing the hydrostatic pressure on the bubble, to avoid diffusion of the gas in the liquid, not that of creating a negative pressure inside the bubble, i.e. a pressure lower than the pressure in the surrounding medium.

Thus, Van Liew does not disclose or suggests gas bubbles having a gas pressure lower than the atmospheric one.

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Applicants respectfully disagree. Like the '809 patent and the Van Liew article, the cited patents and applications fail to teach or suggest contacting dried material with a gas at reduced pressure as required by the instant claims. Thus, the cited combinations cannot render Applicants claims obvious. Thus, Applicants request that the double patenting rejections be withdrawn.

### CONCLUSION

Applicants submit that the pending claims are allowable. If any questions remain, Applicants invite the Examiner to contact Applicants undersigned attorney. No fees are believed due in connection with the filing of this Response to Restriction Requirement. However, the Director is hereby authorized to charge any required fees and credit any overpayments to Deposit Account No. 50-2168.

Respectfully submitted,

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